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Vascular calcification: Hardening of the evidence

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In the past several years, basic-science studies have shown that vascular calcification is an active, cell-mediated process. It is increased in the uremic milieu and with hyperphosphatemia and therefore should be preventable. Additional advances in imaging techniques have facilitated the diagnosis of arterial calcification, a critical initial step in the translation of this knowledge to patient care.

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In the past ten years we have observed a major increase in the number of publications that examine vascular calcification in chronic kidney disease (CKD) patients, especially those receiving dialysis. Using the limited search terms 'vascular calcification' and 'kidney/renal' in PubMed, there were 11 articles in 1995 and 115 in 2005. Yet this issue is not new; studies in the 1970s clearly demonstrated that calcification in the intimal and medial layers of arteries was increased in patients with advanced kidney disease.[1] Why has there been such an increase in interest in this field recently? There are several likely reasons. First, advances in basic-science research have demonstrated that vascular calcification is not just the passive process we once thought. Vascular smooth muscle cells retain pluripotential capability and can transform into osteoblast-like cells. These cells, at least in culture, can produce bone matrix proteins and will mineralize in the presence of calcium and phosphorus at levels common in CKD patients. Furthermore, uremic serum, oxidized proteins, low fetuin-A, interleukin-1, and interleukin-6 can all accelerate this process[2] (Table 1). Observational studies have also shown these same factors to be associated with increased mortality in dialysis patients and, in some studies, with increased vascular or valvular calcification.[3,4] Second, a major advance in technology has led to our ability to quantify the degree of calcification in a noninvasive manner with computed tomography (CT) scanners, either electron beam CT or multislice CT. This has allowed us to conduct observational and interventional studies that have greatly enhanced our understanding of the pathophysiology of the calcification process and the extremely high incidence of coronary artery, aorta, and valvular calcification. Nearly all series in dialysis patients from all over the world demonstrate that 70% of patients have significant calcification of the coronary arteries and aorta, and nearly 50% have valvular calcification.[5] Even 50% of patients new to dialysis have evidence of significant coronary artery calcification.[6] Third, our once complacent acceptance of serum phosphorus levels of 7 mg/dl has been replaced by new knowledge that disorders of mineral metabolism and bone contribute to morbidity and mortality beyond fractures and bone pain. This recognition of the systemic nature of this problem led Kidney Disease: Improving Global Outcomes to coin the new term 'CKD–mineral bone disorder' (CKD–MBD) to describe the trilogy of abnormal biochemistries, bone, and extraskeletal calcification, while reserving the term 'renal osteodystrophy' to describe pathology limited to bone.[7] Lastly, clinicians now have many new therapeutic options to treat CKD–MBD, one of which, sevelamer, has been shown to ameliorate coronary artery and aorta calcification in two randomized prospective trials.[6,8]

How has this new knowledge changed the care of our patients? Recent clinical practice guidelines have attempted to guide the approach and the treatment of our patients using evidence ratings. The Kidney Disease Outcomes Quality Initiative bone and mineral guidelines, published in 2003, recommended more aggressive lowering of serum phosphorus calcium × and × phosphorus product. These guidelines also opined that there were some data, albeit not strong, to recommend that the amount of oral calcium in the form of phosphate binders be restricted to 1500 mg per day, and that calcium binders not be used in dialysis patients with low parathyroid hormone or evidence of vascular calcification in order to reduce the burden of calcification.[9] These recommendations were based on opinion, with a literature review cutoff of 2001. These guidelines also did not detail how to diagnose vascular calcification, or how to quantify the severity. The Kidney Disease Outcomes Quality Initiative cardiovascular guidelines, by a separate work group, recommended that screening for vascular calcification should be done, and that, if found by plain radiographs, calcification at another site should be sought (level C = weak evidence or opinion). These guidelines, published in 2005, further recommended that if vascular calcification is present at two or more sites, then consideration should be given to prescription of a non-calcium-containing phosphate binder (level B = moderately strong evidence). Both of these sets of guidelines lack definitive information on the sensitivity, specificity, and predictive value of these various noninvasive measures of arterial calcification. A consensus conference of international experts in the field of mineral and bone metabolism and vascular calcification, held in 2003, concluded that a calcification index should be developed.[10] It was believed that such an index would

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Table 1 | Risk factors for vascular calcification, identified in human, animal, or *in vitro* studies

Clinical	Age
	Duration of dialysis
	Kidney function/Uremia
	Diabetes
	Known coronary artery disease
	Abnormal bone
Biochemical	Hyperphosphatemia
	Hypercalcemia
	Abnormal parathyroid hormone
	Low fetuin-A
	Elevated cytokines
	Oxidative stress
	Low pyrophosphate
	Decreased MGP
	Decreased BMP-7
Medications	Calcium-containing phosphate binders
	High-dose vitamin D
	Coumadin (decreases active MGP)

MGP, matrix Gla protein; BMP, bone morphogenetic protein.

facilitate the ability of a clinician to diagnose vascular and valvular calcification in order to predict which patients would have adverse cardiovascular outcomes. The conference attendees thought that this would be an important first step to identify the subset of subjects most likely to benefit from aggressive and, unfortunately, expensive interventions.

Bellasi and colleagues[11] (this issue) describe work that is the first step in developing such a calcification index. They performed electron beam CT to quantify coronary artery calcification in 140 dialysis patients in the United States and compared these results with those of tests that are less expensive, more commonly available, and with lower radiation exposure, including pulse pressure, echocardiography, and plain lateral abdominal film. They found a likelihood ratio (95% confidence interval) of a coronary artery calcification score of ≥100 by electron beam CT of 1.79 (1.09, 2.96) for calcification of the aorta or mitral valve, and 7.50 (2.89, 19.5) for a lateral lumbar X-ray score of ≥7. In contrast, there was no significant predictive value of pulse-pressure assessment. Although these results are encouraging, it should be emphasized that no area under the curve was above 0.8. These data represent an important first step to aid the clinician in risk stratification of vascular calcification in order to guide therapy. The next study to follow logically would be to evaluate combinations of factors, probably age, duration of dialysis, biochemistries, and one of these tests, to see whether the positive and negative predictive values improve. Most important, patients must be followed prospectively to determine whether this calcification index will predict mortality, and whether interventions that reduce the index lead to improvements in mortality.

It is this last measure that remains the most frustrating to the nephrology community. Our dialysis patient population has dismal survival statistics, worse than those for many cancers, and we have failed to make a significant impact on mortality despite many new advances. Importantly, we lack large, prospective randomized clinical trials to guide clinical decision making, a luxury that so many other fields in medicine enjoy. Why is this so? One explanation is that many studies are simply underpowered. A second explanation is that the population of dialysis patients is relatively small compared with that for other diseases, which reduces the funding available to conduct such studies. Yet another explanation is that our patients on dialysis have so many problems that we cannot begin to treat all in a single study. The latter point is important, as it is likely that a combination of interventions will be required to reduce mortality. Despite this lack of evidence, we all routinely still provide these interventions to our patients, including enhancement of dialysis dose, correction of anemia, lowering of blood pressure, reduction of low-density lipoprotein with statins, improvement of glycemic control, and reduction of parathyroid hormone, because it makes biologic sense to do so.

So what should we do with the hardening of the evidence on vascular calcification? The study by Bellasi and colleagues[11] suggests that we can use simple screening tools to give us a roughly 70% chance of predicting significant coronary artery calcification in our dialysis patients. We can then choose to use those data in a number of ways, none of which will be strongly evidenced based. First, we can use the presence or absence of calcification to guide our choice of phosphate binders. Second, we can use the presence or absence of calcification to educate our patients on the need to be compliant with phosphate binders, antihypertensives, and intradialytic weight gains (to name a few). Third, we can use the presence of calcification to help prioritize which of the many expensive medications to use in our patients. The latter may be particularly important for governments and managed care providers around the world to make informed decisions. For example, some such entities require hypercalcemia to be present in order to justify the use of non-calcium-containing phosphate binders. Given the disconnect between hypercalcemia and vascular calcification, using more physiologically relevant criteria may make sense. Most importantly, we now have a sound rationale for using these noninvasive measures of calcification to define better criteria for study-population inclusion in studies that aim to reduce vascular calcification. Perhaps better-defined populations will lead to better studies, and, ultimately, the Holy Grail of nephrology — a reduction in mortality in dialysis patients.

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Bisphosphonates prevent experimental vascular calcification: Treat the bone to cure the vessels?

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Bisphosphonates are inhibitors of bone resorption that are widely used to treat osteoporosis. Price and colleagues demonstrate that ibandronate suppressed the development of uremia-related vascular calcification in rats. These findings extend the link between bone remodeling and vascular calcification to the context of chronic renal failure, opening perspectives toward novel therapeutic strategies.

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Chronic kidney disease is associated with a strong increase in cardiovascular risk, which is responsible for approximately 50% of the mortality in the hemodialysis population. Increased vascular calcification is a prominent feature of vascular disease in uremic patients. Coronary calcification is already present in young hemodialysis patients and shows rapid progression. In addition to increased calcification of atherosclerotic plaques, patients on dialysis also show characteristic calcifications of the vascular tunica media, which also contribute significantly to the excess cardiovascular mortality observed in uremic patients.[1]

Price *et al.*[2] (this issue) report that the bisphosphonate ibandronate prevents the development of vascular calcification in rats with adenine-induced chronic renal failure maintained on a low-protein diet.

Combination of adenine-induced chronic renal failure with a synthetic diet with low protein content proved to reliably induce media calcification in the large arteries of these animals, whereas the standard model induces vascular calcification only in a subset of animals[3] (V Persy *et al.*, unpublished observations). The availability of a reliable model of uremia-induced vascular calcification is an important asset for future experimental research into the pathomechanisms of pharmacological agents and their impact on artery calcification in chronic renal failure. Moreover, this finding is not without its implications for human disease: dietary protein restriction is still occasionally used in chronic kidney disease patients in order to slow progression of kidney-function deterioration and is one of the standard measures imposed on dialysis patients to keep phosphate levels under control; malnutrition always looms around the corner for these patients. So maintaining a good nutritional status in end-stage renal failure patients is important not only to fight off chronic inflammation, but possibly also to limit the development of vascular calcification.

Bisphosphonates are pyrophosphate analogues resistant to enzymatic hydrolysis that are widely used to treat bone diseases characterized by increased bone resorption, such as osteoporosis, Paget's disease, osteolytic lesions, and hypercalcemia associated with multiple myeloma. In high doses these compounds physicochemically inhibit mineralization by inhibiting the formation and aggregation of calcium phosphate crystals and blocking the transformation of amorphous calcium phosphate to hydroxyapatite. However, their therapeutic use depends on their inhibition of bone resorption, which occurs at low doses that do not affect mineralization.[4] Bisphosphonates increase the bone mineral density of osteoporotic patients by inhibiting osteoclastic bone resorption through several mechanisms: they inhibit terminal differentiation of osteoclasts, induce apoptosis of osteoclasts, and decrease osteoclastic activity by inhibiting protein prenylation.[4]

However, bisphosphonates are also reported to act on cells of the osteoblastic lineage,[5] and the effect of different bisphosphonate compounds on osteoblastic cells correlates well with their different potency *in vivo*.[4]

The findings reported in this issue[2] extend results previously reported by Price's group showing that bisphosphonates can inhibit the development of arterial calcification in rats with normal renal function treated with warfarin or toxic doses of vitamin D,[6] and they add to the growing body of experimental evidence that links vascular calcification to

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